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Abstract: Background: Magnetic Resonance Imaging studies frequently report abnormalities of the cerebellar vermis in schizophrenia, though with some discrepancies as to the nature and location of such abnormalities. Imaging studies typically investigate volumetric differences. Yet substantial evidence supports the hypothesis that scaling relationships control grey and white matter proportions in the mammalian brain. Assuming that proper scale relationships between tissue class volumes of the cerebellar vermis are necessary for healthy functioning, we examined proportional relationships between brain tissue class volumes in the vermis of healthy controls and patients with schizophrenia.

Methods: Measures of grey and white matter tissue volumes from three anatomical divisions of the vermis were obtained from 52 patients with chronic schizophrenia and 55 healthy controls. Cross-correlations of the tissue class volumes were computed for each subject group. The number of significant correlations in each

group were compared. In addition, the grey/white matter ratio was computed within and across each vermian division. Differences in mean and variance were assessed using t- and F-tests. A False Discovery Rate of 0.05 controlled for multiple comparisons.

Results: Among controls, thirteen of fifteen correlations were significant. Among patients, eight of fifteen correlations were significant. Five of the nine grey/white matter ratios had an increased mean in the patient group, and all of the variance were trend level or significantly increased in the patients.

Conclusions: These results show that tissue class volumes in the cerebellar vermis are strongly interrelated in controls, and that these relationships are disturbed in patients with schizophrenia.

Dear Editors,

Please find the manuscript "Grey and white matter scale relationships in the cerebellar vermis altered in schizophrenia" with this submission. The underlying conjecture of the paper is that relative volumes of different tissue types in a healthy brain are constrained by biological factors, and that disruption of these relationships is an important aspect of neuropathology. We focus our investigation on the cerebellar vermis, as growing evidence suggests that the cerebellum is involved in cognition and that vermis morphology is altered in schizophrenia. We believe that it is the first work to thouroughly investgate relationships between vermis tissue volumes in controls, and how these relationships might be altered in schizophrenia.

We tested the conjecture by cross-correlating grey and white tissue volumes in three regions of the vermis and by computing grey/white matter ratios in and between these regions, in healthy controls. The same analysis was performed on the patients. The measures appeared to be quite strong in the controls. Many were significantly altered in the patients. Inter-regional correlations (such as anterior superior grey matter to posterior superior grey matter) were most affected in the patients, while intra-regional correlations were much less affected. This allows speculation that overall loss of balance between tissue types is more disruptive than local reductions.

The current investigation was based on tissue volumes segmented into grey and white matter. A previous publication from our group[1] used the same volumes, unsegmented, to show that the patients had significantly reduced volumes compared to the controls. While the two studies are related, they differ in hypothesis, analysis, and discussion of the data.

Sincerely,

Glenn Lawyer*, Ragnar Nesvåg, Katarina Varnäs, and Ingrid Agartz.

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[1] Okugawa G, Sedvall G, Agartz I. Smaller cerebellar vermis but not hemisphere volumes in patients with chronic schizophrenia. *American Journal of Psychiatry.* 2003;160:1614-1617. Included in submission.

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Grey and white matter proportional relationships in the cerebellar vermis altered in schizophrenia

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Key words: cerebellar vermis, proportional relationships, MRI, volumetry, morphometry, schizophrenia

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Abstract

Background: Magnetic Resonance Imaging studies frequently report abnormalities of the cerebellar vermis in schizophrenia, though with some discrepancies as to the nature and location of such abnormalities. Imaging studies typically investigate volumetric differences. Yet substantial evidence supports the hypothesis that scaling relationships control grey and white matter proportions in the mammalian brain. Assuming that proper scale relationships between tissue class volumes of the cerebellar vermis are necessary for healthy functioning, we examined proportional relationships between brain tissue class volumes in the vermis of healthy controls and patients with schizophrenia.

Methods: Measures of grey and white matter tissue volumes from three anatomical divisions of the vermis were obtained from 52 patients with chronic schizophrenia and 55 healthy controls. Cross-correlations of the tissue class volumes were computed for each subject group. The number of significant correlations in each group were compared. In addition, the grey/white matter ratio was computed within and across each vermian division. Differences in mean and variance were assessed using t- and F-tests. A False Discovery Rate of 0.05 controlled for multiple comparisons.

Results: Among controls, thirteen of fifteen correlations were significant. Among patients, eight of fifteen correlations were significant. Five of the nine grey/white matter ratios had an increased mean in the patient group, and all of the variance were trend level or significantly increased in the patients.

Conclusions: These results show that tissue class volumes in the cerebellar vermis are strongly interrelated in controls, and that these relationships are disturbed in patients with schizophrenia.

1 Introduction

Morphological investigations of cerebellar volumetric abnormalities in schizophrenia patients primarily implicate the cerebellar vermis. A number of Magnetic Resonance Imaging (MRI) studies have indicated vermal abnormalities in patients compared to controls, while reporting that differences in cerebellar hemispheric volumes were non-significant (1; 2; 3; 4; 5; 6). Similar results have been found by our group, in a study restricted to men (7) and in a study comparing 59 patients with schizophrenia to 57 matched controls (8).

Yet despite general agreement in these studies that disturbance of some type exists, the nature of the disturbance is not consistent. Most of the just cited studies found smaller vermis volumes in regions of the vermis (2; 3; 4; 5; 7; 8). The studies differ, however, in which regions of the vermis show such difference. Two studies (1; 6) which segmented the vermis into grey and white matter both found increased white matter in the patients. Additional studies question the existence of vermian reduction in schizophrenia (9; 10; 11).

Insight into both the nature and functional significance of vermian disruption in schizophrenia may be gained by investigating proportional relationships between grey and white matter tissue volumes. Brain developmental mechanisms in healthy individuals of any mammalian species must strike a balance between the strongly interacting factors of the number of neurons, the number and speed of inter-neuron connections, physical space restrictions, and metabolic costs. These factors are hypothesized to dictate a species-specific optimal isocortical architecture (12; 13). This optimal architecture would be evidenced by proportional relationships between tissue types within individ-

uals of a given species, or as scaling laws relating tissue type volumes across species. Indeed, such relationships are frequently observed. Strong correlations between total brain volume and grey matter volume have been reported in healthy human subjects (14), an effect which appeared to be independent of gender. Many measures, including isocortical thickness (15), white matter volume (15), and number of connections between cortical areas (16) follow exponential scaling laws as isocortical size increases across mammalian species. The requirement for compact inter-neuronal wiring has been used to explain cortical folding patterns in primates (17), and may also dictate the layout of cortical areas (18).

The constraints which dictate proportional relationships in the isocortex also apply in the cerebellum. In a simplified model where grey matter processes information locally and white matter transmits both the inputs and outputs of this processing, the theory predicts that grey matter and white matter volumes in an anatomically distinct brain structure would have a proportional relationship. The vermis can be subdivided along major fissures into three regions, the anterior superior (lobules I–V), posterior superior (lobules VI–VII) and posterior inferior (lobules VIII–X) (see Figure 1). This division has been used in a number of studies of the vermis (1; 2; 4; 5; 8). The major fissures which separate these divisions, along with the general lack of associative connections in the cerebellum (19; 20), suggests that these divisions are anatomically distinct. The just postulated model predicts that grey and white matter tissue volumes within each of these divisions would be strongly correlated in healthy subjects. Correlations across regions would, under the model, suggest the presence of extra-vermian neuronal circuitry which required balanced input from several vermian regions. The model further postulates that proper function

depends on a proper balance between tissue types. A smaller yet properly proportioned vermis may not lead to noticeable functional impairment, while a vermis with disturbed proportions, even if normal-sized, would, under the model, would. This suggests that vermian disruptions in schizophrenia may be characterized by alterations in correlations between tissue volumes.

The aim of this study was to examine proportional relationships in and between grey and white matter tissue volumes in the cerebellar vermis of healthy individuals, and investigate if these relationships were altered in schizophrenia. The guiding hypothesis was that cerebellar vermis tissue volumes in healthy individuals are governed by strict scaling requirements, and that these proportional relationships would be disturbed in schizophrenia.

2 Materials and Methods

2.1 Subjects

Subject recruitment and scan acquisition were conducted as part of the HUBIN project (21; 22) at Karolinska Institutet, Stockholm, Sweden. Subjects in this study were unrelated Caucasian individuals living in Stockholm county in Sweden. The patients were chronic, stable, medicated people recruited from outpatient clinics in the Stockholm region. Control subjects were recruited from a general population register and from hospital staff. Exclusion criteria for all subjects included a current diagnosis for alcohol or drug usage disorder, head trauma with loss of consciousness for more than 5 minutes, or severe somatic disorder. Additional exclusion criteria for the controls were current or past treatment for a psychiatric disorder or first degree relatives with a

psychotic disorder. All subjects completed a structured clinical interview by a trained psychiatrist to confirm diagnosis or lack thereof. All subjects were found to be healthy after physical exams and blood and urine tests. Recruitment and diagnostic procedures used in the HUBIN project have been more thoroughly described in (23; 24).

Data on the vermis was available on a large subset of the HUBIN material. This included 55 healthy control subjects (37 men, 18 women) and 52 patients (33 men, 19 women) with established schizophrenia (n=43) or schizoaffective disorder (n=9) according to DSM-III and DSM-IV criteria. The mean age of the patients was 42 ± 7.0 years, and mean duration of illness was 15.3 ± 7 years for men, 13.2 ± 7.8 years for women. The mean age of the controls was 37 ± 8.8. A previous analysis of this subject material determined that there was no significant difference in age between the patient and control groups, both with and without respect for gender (8).

2.2 Scan acquisition and processing

Both T1- and T2-weighted Magnetic Resonance images (MRI) were acquired from each subject, under the following parameters. T1: 1.5-mm coronal slices, no gap, flip angle=35 degrees, TR=24 msec, TE=6.0 msec, number of excitations=2, field of view=24 cm, acquisition matrix=256x192. T2: 2.0-mm coronal slices, no gap, TR=6000 msec, TE=84 msec, number of excitations=2, field of view=24 cm, acquisition matrix=256x192. Scans were acquired using a 1.5 Tesla GE Signa (GE, Milwaukee, Wis, USA) system at the Magnetic Resonance Research Center, Karolinska Hospital, Stockholm, Sweden, between 1999 and 2003. All scans were inspected by a neuroradiologist and found to

be free of pathological defects.

The MR images were processed using the BRAINS software (25; 26) following published lab manuals. Each image was aligned to Talairach space. The tissue class composition of each voxel was determined by multi-spectral discriminant analysis (27). This process estimates the percentage of each tissue class type in each voxel, which compensates for partial voluming effects. The tissue segmentation was used to create a segmented image with the same alignment as the T1 and T2 images.

Manual tracing, conducted using the aligned T1, T2, and segmented images, was used to outline three regions of the cerebellar vermis: anterior superior (AS, lobules I–V), posterior superior (PS, lobules VI–VII) and posterior inferior (PI, lobules VIII–X). These are shown on a mid-sagittal image in Figure 1. The tracing followed established anatomical landmarks (7; 8). The entire vermis was traced, generally extending 5 slices on either side of the mid-sagittal plane. The lateral boundaries were defined by the sagittal slice on which the primary fissure and horizontal fissure disappeared from the image. Two individuals, both post-doctoral researchers with advanced degrees in psychiatry, performed the tracing (IA and GO). Inter- and intra-rater reliabilities for the volumetric measurements of non-segmented anterior vermis, posterior superior vermis, and posterior inferior vermis were quite high, with the lowest intra class correlation being 0.95 as measured using 10 randomly selected scans (8). Grey and white matter tissue volumes were measured for each structure by summing the percentage of the tissue in each voxel within each vermian region.

2.3 Statistical analysis

Cross-correlations of the grey and white matter tissue volumes of the three vermian regions were computed separately for patients and controls. Cross-correlating six measures (3 regions x 2 tissue types) resulted in fifteen informative correlations for each subject group. The significance of each of these correlations was computed using Pearson's rho. Correlations significant in one group but not the other were identified, and the total number of significant correlations in each group was counted. Fisher's Z was used to test if the individual correlations differed between groups.

To quantify the proportional relationships, grey to white matter tissue volume ratios were computed for each subject. Ratios were computed both within and across the subdivisions of the vermis. This resulted in three intra-region ratios (grey/white matter in the AS, PS, and PI vermis) and six inter-region ratios (AS grey/PS white matter; AS grey/PI white; PS grey/AS white; PS grey/PI white; PI grey/AS white; PI grey/PS white). The mean and variance of these ratios were computed separately for the patients and the controls. A two-tailed heteroscedatic t-test was used to test for difference in means. An F-test was used to test for difference in variances.

To test for more general scaling relationships, the ratio of each tissue type to the total vermis volume was computed. The mean and variance of these ratios were computed separately for the patients and the controls. A two-tailed heteroscedatic t-test was used to test for difference in means. An F-test was used to test for difference in variances.

The study's main hypothesis was that the controls would exhibit a strong cor-

relation structure, and that this structure would be disturbed in the patients. Evidence for or against this hypothesis was provided by the large number of supporting tests. As a small number of false positives in the supporting tests would not change inference regarding the main hypothesis, Benjamini's False Discovery Rate (FDR) (28) was used to determine a significance threshold properly compensating for the 60 comparisons (15 correlations in each of 2 groups + 15 Fisher's Z + 9 inter/intra-regional ratios + 6 total volume ratios). The FDR procedure is robust against positive dependencies between the tests (29), such as those in our analysis. Significance was defined as a false positive rate of 0.05, i.e. one in twenty of the reported positive test results can be expected to be false. Strong significance was defined as a false positive rate of 0.01.

The grey and white matter tissue volume measurements and their ratios were tested for normality using the Shapiro-Wilks test. Outliers, defined as samples more than 1.5 times the interquartile range above the third quartile or below the first quartile, were identified. The tests for normality and outliers were made separately on the patients and on the controls. The group comparisons of the correlations, the mean and variance of the ratios, and the tests for normality were repeated with outliers removed.

A preliminary analysis using Pearson's rho found that age and tissue volumes were significantly ($p < 0.01$) negative correlated in the controls, but not in the patients. Correlations between age and intra-regional tissue volume ratios were also significant in controls, but not in the patients. The measured correlation coefficients and p-values can be seen in Table 1.

It was decided not to control for age effects in the main study for several

reasons. Age effects were only present in the control subject group. Controlling for age would lessen the variance in the controls, making any cross-correlations in the tissue volumes of this group more significant. Not controlling for age can thus be seen as a conservative approach. We also note that there were no significant age differences between the two groups.

Additional preliminary analysis used Pearson's rho to test for correlations between duration of illness and tissue volumes in the patients. No significant correlations were found.

All statistical analysis was made using the R software package (30).

3 Results

The correlation structure was strong in the controls, and weakened in the patients. Among controls, twelve of the fifteen measured correlations were strongly significant in the FDR sense, and one additional correlation was significant. The non-significant correlations were the PI grey to AS white matter (p-value of 0.35) and PI grey to PS white matter (p-value of 0.03). Among patients, eight of the correlations were strongly significant in the FDR sense. These included all of the intra-regional grey to white matter correlations, all of the inter-regional white to white matter correlations, the AS grey to PI grey matter correlation, and the AS grey to PI white matter correlation. The remaining correlations were not significant.

All correlations were positive with the exception of the non-significant PS grey to PS white matter correlation in patients (corr. coef. -0.04). Tables 2 and 3 show the significance values for the controls and patients, respectively.

Fischer's Z tests indicated that three of the measured correlation coefficients differed significantly between patients and controls. These were between the PS grey and three other measures: AS grey (p-value of 0.002), AS white (p-value of 0.006), and PI white (p-value of 0.003). Table 4 shows the results of the Fisher's Z tests.

Significance was defined as uncorrected p-values at or below 0.017, which the FDR procedure suggested would result in no more than 5% falsely positive correlation tests. Strong significance was defined by the FDR procedure as p-values at or below 0.005. While Bonferroni correction is probably too strict given the dependencies between the measures, it is worth noting that eleven of the correlations in the controls remained significant at an alpha of 0.01 after Bonferroni correction for the 30 tests of correlation. Five of the correlations in the patients remained significant at an alpha of 0.01 after Bonferroni correction for 30 tests.

Patients had strongly significant higher mean grey/white matter ratios compared to controls in the AS and PS vermis. Patient had strongly significant higher inter-region mean AS/PS, PI/AS, and PI/PS grey/white matter ratios. None of the other ratios had a significant difference in mean value. Patients had significant, and generally strongly significant, higher variance in grey/white matter ratios for all measured ratios except the intra-region AS and PS, which showed a trend towards significance (p-values of 0.03 and 0.02, respectively), and the inter-region PI/AS grey/white matter ratio (p-value 0.07). Results for the ratios are given in Table 5

Patients had significantly different ratios of tissue volume to total vermis volume for all measures except PI white matter, which was identical in both

groups. The AS grey and PI grey matter, as a portion of the total vermis, were increased in patients, while the proportions of AS white, PS grey, and PS white matter were decreased. The only significant difference in variance in these ratios was the PS grey, which had less variance in patients compared to controls. The measures are shown in Table 6.

Outliers were found for the following measures. AS white matter had 1 patient and one control outlier, PS grey had 3 patient outliers, PS white had 1 control outlier, and PI white had 1 patient and 4 control outliers.

The Shapiro-Wilks test indicated that the assumption of normality was reasonable for all of the patient measures, with the possible exception of the PS grey (p-value of 0.049). When the three outliers were removed, the patient PS grey appeared normal (p-value of 0.30). The assumption of normality was reasonable for the controls, with the exception of the PI white matter (p-value of 0.03). When the 4 outliers were removed, the Shapiro-Wilks test did not quite reject the null hypothesis that the data represented a normal distribution (p-value of 0.052).

Removing the outliers did not change which correlations were significant, nor did it change which ratios had significantly different means. After removing outliers, none of the differences in correlation coefficients were significant. Differences in variance between patients and controls were no longer significant for the PS/AS and PS/PI grey/white matter ratios. Difference in variance became significant for the ratio of PI white matter to total vermis volume. As removing outliers had minimal effect on the overall results, all tables and results shown refer to the complete data, including the outliers.

4 Discussion

The main finding was that grey and white matter volumes within and across vermal regions were strongly correlated in control subjects and markedly less so in patients with schizophrenia. The finding of strong intra-region grey to white matter correlations in the controls was consistent with a theory of biological constraints between grey and white matter volumes in anatomically distinct brain structures. The strong inter-regional correlations, however, were less strongly predicted as there is no direct neurological connectivity between the different divisions of the vermis defined here (19; 20). This encourages speculation that the inter-regional correlation in the controls could be modulated by constraints involving the needs of a larger brain circuit. The present results would not help settle the debate between those who hold that that cerebellar function is limited to motor control and motor learning (31; 32; 20) and those who find evidence suggesting that cerebellar structures play a role in cognition and affect (33; 34; 35; 36).

The Fisher's Z tests showed that the direction of most of the correlations were similar in both patients and controls. To the extent that the correlations reflect biological constraints, this suggests that the same constraints were operating in the patients as in the controls.

The weakening of correlational structure in the patients was limited to the inter-regional correlations. None of the inter-region grey to white matter correlations were significant, and only one of four inter-regions grey to grey matter correlations were significant. The three correlation coefficients which differed between the two groups were all inter-regional. All intra-region grey

to white matter correlations, however, were strongly significant. The lack of inter-region grey matter correlations combined with the preservation of intra-region correlations in the patients studied here allows for speculation that loss of global coherence between vermian tissue volumes, rather than localized smaller volumes, may contribute to the cognitive abnormalities characteristic of the disease. The weakening of inter-regional correlations could be interpreted to support the cerebellar-thalamic-cortical network hypothesized in theories of cognitive dysmetria (37; 33). A relationship between cerebellar dysfunction and both motor and cognitive deficit in schizophrenia also hints at the existence of such connections (38).

While intra-region correlations were preserved in the patients, the intra-region ratios were not. Patients had strongly significant higher grey/white matter ratios in the AS and PS vermis, and a trend towards greater variance of this ratio in all three regions of the vermis. This agrees with observations made by (6).

Previous work has found disturbed proportional relationships in schizophrenia. One study observed an increase in the proportion of nitric oxide synthase immunoreactive Purkinje cells in schizophrenia patients (39). Grey/white matter tissue volume proportions were altered in the striatum of patients with schizophrenia, though the total volume of each structure showed no difference between patients and controls (40). A study of cortical volumes found that patients with schizophrenia had weaker intra-frontal correlations (41) and stronger positive and weaker negative fronto-temporal inter-correlations (42) in comparison to healthy controls. Given that both the number of synapses per neuron (15) and neuron density (43) normally scale with grey matter volume, the observation of reduced neuropil in schizophrenia patients (44) can also be

considered disturbed scale.

The existence of vermian reductions in schizophrenia have been debated. A study published in 2000 included an informal review of post-mortem, CT, and MRI based investigations of vermian reductions in schizophrenia (11). The authors reported inconsistency across studies, possibly due to technological and methodological differences or small sample sizes in post-mortem studies. The study included a post-mortem analysis of 12 patients and 12 controls, and found no significant group differences in vermis volumes. It concluded that the concept of cerebellar atrophy in schizophrenia patients was premature. A contemporaneous post-mortem investigation of six subjects with a very bad outcome and six healthy controls found no significant difference in vermis volumes between the two groups (9).

More recent MRI studies, with presumably better image resolution than the studies reviewed in (11), more consistently observed vermian abnormalities in schizophrenia. A search of Pub Med performed in November 2007, using the search terms "vermis" and "schizophrenia", limited to studies published after 1/1/1999, returned 42 results. Of these, ten contained comparisons of vermis volumes between patients and controls, not counting the just discussed review (11) and papers covered in that review. All ten were based on MRI imaging. Four of these were from our group, and contained overlapping subject samples. These studies consistently found volumetric reductions in patients compared to controls (7; 8; 36; 45). Four additional, independent studies also found reductions in patients compared to controls (2; 4; 3; 5). One study found volumetric reductions only in patients co-morbid for alcohol abuse (10). Two studies found increased vermian white matter volume in the patients (1; 6). These studies are listed in Table 7.

The discrepancy between reductions observed when grey and white matter were not differentiated (4; 3; 5; 8), and white matter increases when tissue type was considered (1; 6) is difficult to explain. A post-hoc analysis of our data found that the mean unnormalized white matter volumes were reduced in patients. T-tests indicated that the differences were not likely to be due to chance (uncorrected p-values: AS $p < 0.001$; PS $p < 0.001$; PI $p = 0.002$). No difference in white matter between patients and controls was found in (10) , absent co-morbidity.

One possible explanation lies in differing definitions and measures of vermian white matter. The previous studies measured white matter volume alternately as a specific region (1) using 1.5 mm voxels, automated tissue segmentation within manually traced regions using 1.5 mm voxels (10), or using voxel-based Bayesian model with a post-processing resolution of 2 mm (6). The current study used 1.5 mm voxels which could contain mixtures of tissue types. The measures in the different studies may also vary due to differing scan/slice alignment protocols. Different normalization routines would also affect the measures. Observed white matter differences in (6) became more significant when volumes were normalized to cerebellar volume.

Age and illness duration effects could also play a role. Significant correlations between age and white matter volumes were observed in our healthy control subjects, but not patients. Results for control subjects were not reported in (6), but it was noted that correlations between age and white matter volume were non-significant in patients. Whole-brain grey/white matter tissue volume ratios are age varying (46; 47), declining linearly from 1.3 at age 20 to 1 at age 50, and then jumping to 1.5 at age 100. The mean subject age in our data was just under 40 years (patients and controls combined), while it

was just under 32 years in (6). Subjects in (1), however, had mean age of just under 38 years, and in (10) 45.5 years.

We did not observe any correlations between tissue volumes and duration of illness, while (6) reported a significant positive correlation between white matter volume and duration. It has been observed that correlation between duration and Purkinje cell size trend towards significance (48).

It has been suggested that schizophrenia may make patients more susceptible to alcohol-related volumetric loss in the vermis (10). Effort has been made to control for possible confounding effects of alcohol in the subjects studied here. The patients were all under long-term care, and none had a current alcohol abuse or dependence diagnosis (8). A follow-up study of alcohol usage in a subset of the subjects used showed that alcohol usages was unlikely to be a confounding factor (45). In reference to the just discussed discrepancies between our findings and those of (6), that study also excluded subjects with a current diagnosis of alcohol or drug dependence. Alcohol was not mentioned in (1).

One significant limitation of this study lies in the accuracy of the tissue segmentation. The vermis has a highly convoluted nature. This is likely to produce partial voluming effects which the image processing software cannot perfectly resolve. While the measures used have been fully validated in cortical areas, their reliability in the cerebellum is not beyond question. It was somewhat comforting to observe the age/tissue volume correlations in the healthy controls.

5 Conclusion

The balance between grey matter and white matter tissue volumes within and between vermian regions were observed to be very strong in healthy controls but disrupted in schizophrenia.

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Financial Disclosures

None

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Fig. 1. Outlines of the anterior superior, posterior superior, and posterior inferior vermis can be seen in the above mid-sagittal image.

Table 1

Correlations between age and tissue volumes and tissue volume ratios in healthy controls and patients with schizophrenia.

	Controls		Patients	
measure	coef	p val	coef	p val
AS total	-0.43	0.001	-0.01	0.92
PS total	-0.54	<0.001	-0.21	0.13
PI total	-0.26	0.05	-0.08	0.59
AS grey	-0.37	0.005	0.00	1.0
AS white	-0.52	<0.001	-0.07	0.64
PS grey	-0.52	<0.001	-0.21	0.13
PS white	-0.55	<0.001	-0.13	0.36
PI grey	-0.21	0.13	-0.08	0.58
PI white	-0.34	0.01	-0.04	0.77
AS g/w	0.42	0.001	0.07	0.62
PS g/w	0.26	0.05	0.00	0.99
PI g/w	0.30	0.03	-0.05	0.73

Abbreviations: AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior; g/w = grey to white matter ratio.

Table 2

Significance of correlation between white and grey matter volumes of the cerebellar vermis in controls. Results deemed non-significant at a False Discovery Rate of 0.05 are shown as 'n.s.'

	AS white	PS grey	PS white	PI grey	PI white
AS grey	< 0.0001	< 0.0001	0.0002	0.0001	0.0090
AS white		< 0.0001	< 0.0001	n.s.	0.0025
PS grey			< 0.0001	< 0.0001	0.0001
PS white				n.s.	< 0.0001
PI grey					0.0002

Abbreviations: AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior.

Table 3

Significance of correlation between white and grey matter volumes of the cerebellar vermis in patients. Results deemed non-significant at a False Discovery Rate of 0.05 are shown as 'n.s.'

	AS white	PS grey	PS white	PI grey	PI white
AS grey	< 0.0001	n.s.	n.s.	0.0014	0.0005
AS white		n.s.	< 0.0001	n.s.	< 0.0001
PS grey			< 0.0001	n.s.	n.s.
PS white				n.s.	0.0041
PI grey					< 0.0001

Abbreviations: AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior.

Table 4

Fisher's Z scores for a difference in correlation coefficient between patients and controls. A † indicates significant difference.

	AS white	PS grey	PS white	PI grey	PI white
AS grey	n.s.	0.002	n.s.	n.s.	n.s.
AS white		0.006	n.s.	n.s.	n.s.
PS grey			n.s.	n.s.	0.003
PS white				n.s.	n.s.
PI grey					n.s.

Abbreviations: AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior.

Table 5

The mean and standard deviation of grey/white matter tissue volume ratios for controls and patients, and significance levels for a difference in mean (t) and variance (F) between these measures. FDR suggests an alpha of 0.01 will result in less than 5% false positives.

AS	6.43 (1.32)	7.83 (1.77)	<0.001	0.03
PS	7.43 (1.19)	8.64 (1.71)	<0.001	0.009
PI	7.82 (1.83)	8.56 (2.56)	0.09	0.02
AS/PS	11.67 (2.37)	17.06 (4.74)	<0.001	<0.001
AS/PI	13.34 (3.39)	14.94 (4.85)	0.05	0.01
PS/AS	4.14 (0.88)	4.11 (1.27)	0.89	0.008
PS/PI	8.52 (1.92)	7.86 (3.01)	0.18	0.001
PI/AS	3.87 (1.11)	4.61 (1.43)	0.004	0.07
PI/PS	6.94 (1.66)	9.86 (2.69)	<0.001	<0.001

Abbreviations: AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior.

Table 6

The mean and standard deviation of the ratio of each tissue volume to total vermis tissue volume, for controls and patients, and significance levels for a difference in mean (t) and variance (F) between these measures. FDR suggests an alpha of 0.01 will result in less than 5% false positives.

Struct	Controls	Patients	t	F
AS grey	0.39 (0.02)	0.42 (0.03)	<0.001	0.03
AS white	0.06 (0.01)	0.06 (0.01)	0.009	0.75
PS grey	0.25 (0.02)	0.22 (0.03)	<0.001	0.006
PS white	0.03 (0.01)	0.03 (0.01)	<0.001	0.45
PI grey	0.23 (0.03)	0.24 (0.03)	0.008	0.6
PI white	0.03 (0.01)	0.03 (0.01)	0.98	0.17

Abbreviations: AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior.

Table 7

Results from the MRI based studies of the vermis cited in this manuscript.

Source		#patients/controls	Results
Levitt et al. 1999	(1)	15/15	total white volume inc.
Nopoulos et al. 1999	(2)	65/65	Cross section of AS red.
Loeber et al. 2001	(3)	19/19	total vermis volume red.
Ichimiya et al. 2001	(4)	20/20	total vermis volume red.
Joyal et al. 2004	(5)	38/26	total vermis volume red., AS* and PS area on mid-sagittal slice red.
Lee et al. 2007	(6)	40/40	total white volume inc.
Okugawa et al. 2003	(8)†	59/57	Total, AS, PS, and PI volumes red.
Sullivan et al. 2000	(10)	46/61	Volume red.*

*Only when co-morbid for alcohol.

†(7; 36; 45) contained subsets of the subjects studied in (8), and are not included in the table.

Abbreviations: inc. = increased; red. = reduced; AS = Anterior Superior; PS = Posterior Superior; PI = Posterior Inferior.

Figure

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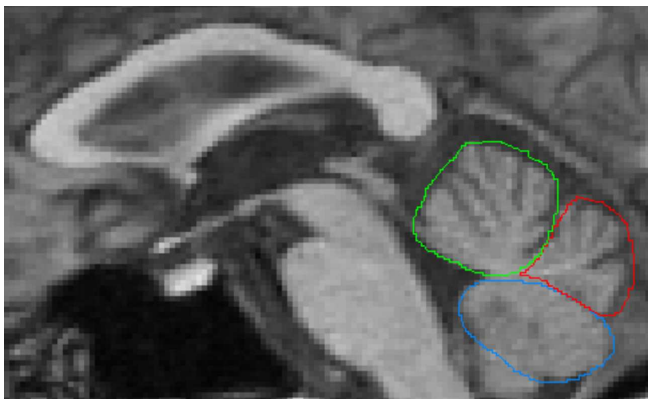

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